Long-term weight loss and improved intermediate cardiovascular outcomes associated with a Mediterranean-style diet in high-risk participants with diabetes: findings from the Heart Healthy Lenoir Project

by

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Abstract

Objective

To determine whether a lifestyle intervention promoting a Mediterranean-style diet and physical activity results in improved lifestyle behaviors and weight loss among participants residing in the "stroke belt" of the Southeastern United States, where the rates of cardiovascular disease are disproportionately high, particularly among people with diabetes and African Americans.

Research Design and Methods

The study was designed as a two-year prospective cohort study to evaluate the lifestyle intervention with an embedded randomized controlled trial (RCT) of a maintenance weight loss intervention during the second year. There were three phases of the study. Phase I (6 months long) was an individually-tailored lifestyle intervention promoting a Mediterranean-style dietary pattern and increased walking. Phase II (also 6 months long) included an optional 16-week weight loss intervention for participants whose BMI was at least 25 kg/m^2 or a maintenance of lifestyle intervention for all others. Phase III (12 months long) included optional participation in a maintenance of weight loss RCT for participants who lost at least 8 lbs or the maintenance of lifestyle intervention for all others. The Phase II weight loss intervention was offered in two formats: 16 weekly group sessions or 5 group sessions and 10 phone calls. Changes in lifestyle behaviors, physiologic cardiovascular intermediate outcomes, and weight were assessed at 6, 12, and 24 month follow-up visits and analyzed to determine differences by diabetes status and then by race within those groups.

Results

Baseline characteristics (n=339): mean age 56, 77% female, 65% black, 37% had diabetes; mean weight was 103kg for those with diabetes, 95kg for those without diabetes. Outcomes: Participants with diabetes reported increased walking and activity times at 24 months, particularly among blacks. Systolic and diastolic blood pressures were reduced by over 8 mmHg at 24 months among black participants with diabetes. Participants with diabetes demonstrated greater weight loss than those without diabetes; those with diabetes lost an average of 1.2 kg, 1.5 kg, and 3.7 kg at 6, 12, and 24 months, respectively. The intervention was highly acceptable in this population.

Conclusions

Overall, participants with diabetes achieved a 3.7 kg sustained weight loss at 24 months. The study interventions also led to improved blood pressure, physical activity, diet quality, and a trend toward improvement in hemoglobin A1c among participants with diabetes. Further study of the lifestyle intervention is warranted with a RCT.

Introduction

The Southeastern United States, particularly the "stroke belt," has high rates of cardiovascular disease (CVD),[1-4] attributed in part to the fact that residents are more likely to be of low socioeconomic status, obese, and sedentary.[5-7] African Americans also have increased rates of cardiovascular disease[3,4,8] and are more represented in the Southeastern United States. The diet in the Southeast also tends to be less healthful compared to other areas of the United States,[9-11] which further contributes to the observed higher rates of obesity, diabetes, and CVD.[12,13]

Several studies have been published looking at lifestyle interventions to promote weight loss and reduce CVD in populations with high rates of diabetes; however many of them did not achieve the desired outcome of CVD reduction. Franz et al. published a systematic review and meta-analysis of lifestyle weight-loss intervention outcomes in adults with type 2 diabetes mellitus.[14] They reported that only the Look AHEAD trial and another Mediterranean diet-based intervention achieved at least 5% weight loss as well as improvement in other intermediate cardiovascular outcomes (blood pressure, lipids, and hemoglobin A1c). Both of these trials also included a physical activity component and frequent contact with healthcare providers.[14] However, Look AHEAD did not actually demonstrate a reduction in CVD events.[15] The PREDIMED trial was the first study to document the ability of a lifestyle intervention to substantially reduce cardiovascular events among participants with and without diabetes; they did so using a Mediterranean diet.[16] One theory for why prior studies such as Look AHEAD[17] and the Diabetes Prevention Program[18] failed to reduce CVD events was because they recommended a low-fat diet as part of their intervention whereas high quality fats are an important factor in reducing CVD.[12] Therefore, a Mediterranean-type diet with high quality fats is a critical component to a lifestyle intervention that successfully reduces CVD.

For these reasons, our group developed a culturally-appropriate lifestyle intervention specifically for a high-risk, racially diverse population like much of the Southeastern United States with a focus on improving diet quality using a Mediterranean-like diet, increasing physical activity, and promoting weight loss. The main results of the Heart Healthy Lenoir Project (HHLP) lifestyle study have previously been published.[19] This paper specifically focuses on how diabetes status and race influence lifestyle and weight loss outcomes as this type of intervention has not previously been studied to determine its effectiveness and acceptability in a largely African American, high-risk population.

Methods

Study Overview

HHLP was a collaborative research effort designed to reduce CVD risk and disparities in risk in Lenoir County, North Carolina. The project consisted of three coordinated studies focusing on lifestyle, high blood pressure, and genomics as they affect cardiovascular risk.[20] The studies were conducted in Lenoir County because of its location in the "stroke belt" with rates of CVD higher than state and national averages as well as its population that is predominantly lower socioeconomic status and 40% African American.[21]

HHLP lifestyle study participants were recruited from the Lenoir County community as well as from the HHLP high blood pressure study which enrolled participants from local clinical practices.[22] The HHLP lifestyle study was designed and conducted with input from a local community advisory committee[20] and was approved and monitored by the University of North Carolina's Institutional Review Board. Data were collected between September 20, 2011 and November 7, 2014.

The lifestyle study consisted of three phases, depicted in Figure 1. Phase I focused on improving diet quality and increasing physical activity; this phase lasted 6 months and was the same for all study participants. Phase II consisted of 1) a weight loss intervention for participants with a body mass index (BMI) ≥ 25 kg/m^2 who chose to enroll in that arm and 2) a maintenance of lifestyle intervention for participants with a BMI < 25 kg/m^2 and those who declined the weight loss intervention. Phase II also lasted 6 months and immediately followed Phase I. Phase III included 1) a year-long, randomized controlled trial comparing a more intensive and less intensive maintenance of weight loss intervention for participants who took part in the Phase II weight loss intervention and lost at least 8 lbs and 2) a year-long maintenance of lifestyle intervention for all other participants. Prior randomized trials from our group[23-26] have shown that similar formats of lifestyle and weight loss interventions are effective among low socioeconomic status participants, therefore, we opted not to include a control group for Phases I and II. Furthermore, the community advisory committee strongly encouraged a study design in which all participants received "active treatment."

Participants

The goal enrollment was 350 participants based on having an adequate sample for the embedded Phase III maintenance of weight loss randomized trial, as previously described.[19] About 150 participants were recruited from the community and 200 were recruited from the high blood pressure study. High blood pressure study participants were included because of their increased risk for CVD and thus potential to benefit from improved lifestyle behaviors. Participants from the community were recruited through flyers, newspaper articles, television notices, word of mouth, and the study website. The study's screening inclusion criteria were relatively limited in an effort to enroll a representative sample. The criteria were: age ≥ 18 years and interest in improving lifestyle behaviors to reduce cardiovascular disease risk. Screening inclusion criteria for the high blood pressure study were age ≥ 18, being an established patient at a participating practice, and systolic BP ≥ 150 mmHg when assessed during routine care within the prior 12 months. Participants attending the enrollment visit for the high blood pressure study were invited to also take part in the lifestyle study until 200 agreed to do so.

After obtaining verbal informed consent, research staff conducted phone interviews to screen potential participants, as previously described.[19] If eligibility criteria were met, participants were invited to attend an enrollment visit at a central research office or at participating clinics. Written informed consent was obtained prior to collecting baseline measures. Participants were compensated monetarily at each of the enrollment, 6, 12, and 24 month visits, receiving a total of $120 if they attended all visits.

Phase I – Lifestyle Intervention

The lifestyle intervention used in this study is a modification of a previously developed and tested intervention originally developed by Ammerman and colleagues,[27,28] which was subsequently revised to emphasize carbohydrate quality as an important component of a heart healthy diet.[23] Consistent with the evolving literature suggesting regular consumption of foods with high quality fats is also important in reducing the risk of CVD in those with and without diabetes,[16,29-34] this study's dietary intervention was further modified to include a major focus on improving dietary fat quality as well. These changes rendered the HHLP lifestyle intervention dietary pattern very similar to the PREDIMED study's nut intervention arm diet;[16] therefore, HHLP named the dietary pattern the "Med-South diet" because of its intended use in the Southeastern United States.

The intervention format and content have been previously published and described in detail.[19] Phase I included four monthly sessions delivered by a trained counselor administered as hour-long individual counseling sessions or two-hour-long group sessions which were held in the central research office or participating clinics. Participants chose their preferred counseling format. Intervention content and time was largely dedicated to dietary counseling (75%) and the rest (25%) physical activity counseling. Dietary counseling focused on using culturally-relevant content to improve fat quality (such as increasing consumption of nuts, full-fat mayonnaise, and vegetable oils); increase fruit and vegetable consumption; favor fish and poultry to red and processed meats; and minimize sugar-sweetened beverages, desserts, and snacks. Physical activity counseling recommended a goal of at least 7500 steps per day or at least 30 minutes of physical activity at least five days per week. Spouses and friends were also invited to join the counseling intervention sessions. When participants could not physically attend counseling sessions, telephone counseling was offered. Participants also received a pedometer and activity logs to self-monitor physical activity as well as a listing of local community resources for healthy eating and physical activity. Those participants who were co-enrolled in the high blood pressure study also received a home blood pressure monitor and were instructed to measure their blood pressure at least three times per week. Other interventions included in the high blood pressure study were not initiated during Phase I of the lifestyle study for the vast majority of participants who were dually enrolled.

During counseling sessions, participants received dietary counseling and created an individually-tailored action plan with his or her counselor to guide eating behaviors. Dietary tips were given relevant to identified problematic eating behaviors, including recipe suggestions in a Southern-style cookbook that was given to all participants. Time permitting, physical activity was addressed at each session. At the beginning of Sessions 2-4, the counselor and participants reviewed progress made toward previously stated goals.

Phase II – Weight Loss and Maintenance of Lifestyle Intervention

Participants with a BMI ≥ 25 kg/m^2 could choose to take part in a weight loss intervention during the second phase of the HHLP lifestyle study. Those who were not eligible for the weight loss intervention (BMI < 25 kg/m^2) and those who declined the intervention received a maintenance of lifestyle intervention consisting of three phone calls, as previously described.[19] Participants who elected to be in the weight loss intervention arm could choose between two formats: a previously-tested weekly group session format over 16 weeks or five group sessions with ten phone contacts (combination intervention), also over 16 weeks.

Phase III – Maintenance of Weight Loss and Lifestyle Interventions

Participants who took part in the Phase II weight loss intervention and lost at least 8 lbs could choose to take part in a maintenance of weight loss randomized controlled trial (RCT). All other study participants received brief, quarterly maintenance of lifestyle intervention phone calls (similar to Phase II), as previously described.[19] For the maintenance of weight loss RCT, participants were randomized 1:1 to receive either 36 phone contacts (24 weekly calls over 6 months followed by 12 biweekly calls over 6 months; more intensive intervention) or 18 phone contacts (12 biweekly calls over 6 months followed by 6 monthly calls over 6 months; less intensive intervention).

Measures

Outcome measures were assessed at baseline, 6, 12, and 24 months. Previously validated questionnaires were administered including the Dietary Risk Assessment (DRA) which addresses overall diet quality,[27,35] SF-12 (SF-12 instrument, Quality Metric, Inc., Lincoln, RI) which addresses quality of life, in addition to other assessments of fruit and vegetable intake,[36] dietary fat quality,[37] and physical activity.[38,39] Physiologic measures included blood pressure, total cholesterol, HDL, hemoglobin A1c, blood carotenoids, and weight. Weight was calculated as the average of two measures to the closest tenth pound according to an electronic scale. Height was measured with a portable stadiometer at baseline only to calculate body mass index (BMI). Blood pressure was calculated as the average of three measurements which were recorded at 60 second intervals (Omron HEM-907XL, Omron Healthcare, Lake Forest, IL) after being seating for five minutes. Participants were asked about any adverse events at each follow-up visit.

Statistical analysis

The HHLP lifestyle study size of 350 (based on powering the Phase III RCT) was considered sufficient for the primary descriptive outcome of changes in diet quality at 6 months and the secondary descriptive outcome of changes in diet quality and weight at 12 and 24 months follow-up.

Sample characteristics were summarized using descriptive statistics, with subgroups by diabetes status and race. Outcomes were assessed using pre-post changes by diabetes status and race using paired t-tests for continuous outcomes, McNemar’s tests for binary outcomes, and Chi-squared tests for subgroup analysis when appropriate. Change in weight and percentage of participants who achieved greater than 5% weight loss were also analyzed by diabetes status and then by race within diabetes status. In addition, changes in weight-related outcomes were further analyzed by intervention group; however, the RCT was ultimately underpowered so trends are shown without significance levels. Because age, race, sex, education, and baseline weight are potential confounders for weight loss according to the literature, a linear regression model was performed adjusting for these variables. Finally, questionnaires were administered at the end of each study phase to assess acceptability of the intervention; results were again summarized using descriptive statistics. Participants who became pregnant, had bariatric surgery, or were diagnosed with cancer (excluding non-melanoma skin cancer or localized breast or prostate cancer diagnosed by screening tests) were excluded from analysis. SAS version 9.3 was used for analysis.

Results

Baseline Characteristics

Participants' baseline characteristics, by diabetes status then further categorized by race, are outlined in Table 1. More than one third of study participants had diabetes. The overall average age was 56 years; participants with diabetes were older on average than those without diabetes (59 versus 54 years) and white participants slightly older than black participants (58 versus 54 years). Men, particularly black men, were underrepresented in the sample. More than half of participants did not have any college education; participants with diabetes and black participants were less educated on average than those without diabetes and white participants. Those without diabetes and whites were also more likely to be married or living with a partner compared to others. Most participants had health insurance (74%) and this did not appear to vary by diabetes status or race. People with diabetes were more likely to not work due to health reasons (31% versus 14%) and less likely to be currently employed (34% versus 58%). Black participants were slightly more likely to be currently employed than white participants regardless of diabetes status, though white participants reported higher household incomes on average compared to black participants. Median household income was less than $40,000 overall; less than $20,000 among participants with diabetes.

In terms of cardiovascular risk factors, reported rates of hypertension were very high in the study (86% overall), which may be largely attributed to how participants were selected. Participants with diabetes were more likely to report a history of hypertension (98% compared to 79%); and blacks reported higher rates of hypertension than whites within each subgroup. Participants with diabetes also reported higher rates of prior coronary heart disease and cardiovascular disease;

there were no apparent differences between races. The majority of study participants had high cholesterol at baseline (56%); participants with diabetes were more likely to have high cholesterol (67% versus 49%) and whites were more likely to have high cholesterol than blacks, particularly among those without diabetes (63% versus 42%). There was no apparent variation in smoking by diabetes status or race.

At baseline, overall diet quality and fat quality were similar across diabetes status and race, with an average DRA total score of 27.8 and fat quality screener score of 15.5. Participants with diabetes had slightly higher fruit and vegetable consumption at baseline (average 3.7 servings per day compared to 3.3). Within that subgroup, blacks reported slightly higher fruit and vegetable consumption (3.8 versus 3.3) though whites reported higher fruit and vegetable consumption among participants without diabetes (3.5 versus 3.1). Participants without diabetes reported much higher total walking and total activity time at baseline (mean 105 and 171 minutes per week, respectively, compared to 67 and 112 minutes per week among those with diabetes). Black participants reported longer walking times than whites at baseline within each diabetes status subgroup though there was less of a difference between races for total activity time. Participants with diabetes weighed more on average than those without diabetes at baseline (103 kg compared to 95 kg). Among participants without diabetes, blacks weighed more than whites at baseline (99 kg versus 90 kg); there was no difference in weight between races among participants with diabetes. BMI is similarly reflective of this trend with an average BMI of 38 among participants with diabetes, regardless of race, and an average of 37 among black participants without diabetes and 32 for white participants without diabetes. Systolic blood pressure was similar across all categories, with a slightly higher average for blacks than whites

(138 mmHg compared to 131 mmHg) among participants with diabetes. Among those with diabetes, black participants had higher hemoglobin A1c percentage at baseline than whites (8.0 compared to 7.6). There was no difference between races among those without diabetes. Participants with diabetes had lower total cholesterol levels at baseline (188 mg/dL compared to 196 mg/dL), with HDL slightly lower (51 mg/dL versus 56 mg/dL) for those without diabetes. Black participants had slightly higher HDL levels (55 mg/dL versus 43 mg/dL among those with diabetes) and lower total cholesterol levels among those without diabetes (193 mg/dL compared to 200 mg/dL).

Outcomes

Several lifestyle and physiologic outcomes of interest were assessed at baseline and at the end of each of the three study phases (6 months, 12 months, and 24 months). Follow-up rates are outlined in Figure 1 with approximately 75% follow-up after each of the three phases. Follow-up rates were similar between participants with and without diabetes.

Lifestyle outcomes (Table 2) revealed that DRA total score was 4 points higher, representing better diet quality, at 6 months among all subgroups, which was statistically significant. Improvement in DRA total score was maintained at 12 months and 24 months compared to baseline among all subgroups except white participants with diabetes. Fat quality score improved by 1.4 on average at 6 months with no significant difference between subgroups by race or diabetes status. Improvement in fat quality was sustained at 12 and 24 months but only statistically significant among the subgroups with larger sample sizes. Only participants without diabetes reported a statistically significant increase in fruit and vegetable servings per day at 6 month, 12 month, and 24 month follow-up. Summary score for drinks, desserts, and snacks was higher among black participants with and without diabetes.

An increase in walking time was sustained at 24 months only among participants with diabetes, and black participants demonstrated a greater increase in walking than whites within that subgroup. This was also true for total activity time where black participants with diabetes were the only subgroup to demonstrate significantly increased activity time compared to baseline at 24 months.

Several measured physiologic outcomes (Table 3) also improved over the course of the study. Among participants with diabetes, systolic blood pressure was reduced by an average of 6 mmHg at 6 months. This finding was sustained at 24 months with an average drop in systolic blood pressure of 7 mmHg among participants with diabetes. The improvement in systolic blood pressure among participants with diabetes can be largely attributed to the black subpopulation of participants as whites did not demonstrate the same improvement in systolic blood pressure (-0.39 mmHg at 24 months) compared to blacks (-9.29 mmHg at 24 months). There was a similar trend with improvement in diastolic blood pressure over the course of the study. On average, both participants with and without diabetes demonstrated improvements in diastolic blood pressure (-7.18 mmHg at 24 months for participants with diabetes and -6.44 mmHg at 24 months for participants without diabetes). Improvements in blood pressure were approximately equal across races among participants without diabetes however among participants with diabetes, black participants again had greater change in diastolic blood pressure compared to baseline on average than white participants (-8.18 mmHg which was a statistically significant drop compared to -3.33 which was not statistically significant, respectively). There is a trend toward significant improvement in hemoglobin A1c at 12 months among participants with diabetes (-0.30; $p=0.07$). Weight loss was a major outcome of interest. Participants with diabetes had significant, sustained, and progressive weight loss compared to baseline at 6, 12, and 24 months (mean -1.24 kg, -1.53 kg, and -3.67 kg respectively) across all intervention groups. White participants with diabetes appear to have greater weight loss than black participants with diabetes however their weight loss only reached statistical significance at 24 months given the small sample size. Black participants with diabetes appeared to lose the most weight during phase III of the study. Participants with diabetes showed greater weight loss than those without diabetes as participants without diabetes did not have sustained weight loss at 24 months on average, despite showing significant weight loss at 12 months. Sample sizes are too small to provide informative statistics by intervention group though weight loss was similar across intervention groups at 24 months.[19]

After adjusting for age, race, sex, education, and baseline weight, our regression model demonstrated that only participants with diabetes had significant, sustained weight loss at 24 months ($p<0.0001$) and that participants with diabetes had significantly more weight loss on average than participants without diabetes ($p=0.01$).

In addition to measuring average change in absolute weight from baseline, success of the intervention was also measured by calculating percentage of participants who achieved greater than five percent weight loss compared to baseline at each time point. Again, a greater proportion of participants with diabetes demonstrated sustained, >5% weight loss compared to baseline at 24 months compared to those without diabetes (34.4% compared to 16.23%, respectively). Percentages were similar between blacks and whites with diabetes however more black participants without diabetes achieved >5% weight loss at 24 months than whites without diabetes (18.5% compared to 10.0%, respectively).

Acceptability of the interventions was assessed using questionnaires at the end of each study phase. At the end of the lifestyle intervention (Phase I), the majority of participants, regardless of diabetes status or race, felt that the session on nuts, spreads, dressings, and oils was most helpful. The vast majority of participants with and without diabetes either "strongly agreed" or "agreed" that the lifestyle intervention was easy to understand. More participants without diabetes "strongly agreed" that the lifestyle program was easy to understand (65%; compared to 43% with diabetes). Almost all (97%) of participants with diabetes and (98%) without diabetes either strongly agreed or agreed that they would recommend the lifestyle program to others. After Phase II, all participants with diabetes in the group weight loss arm were satisfied or very satisfied with the intervention and 88% of participants with diabetes in the combination weight loss arm were satisfied or very satisfied with the intervention. Participants without diabetes were similarly satisfied with the interventions.

Discussion

The HHLP lifestyle study promotes a Mediterranean-style diet with a focus on fat and carbohydrate quality in a way that is designed to be appealing to residents of the Southeastern United States, particularly in the "stroke belt" where the population's cardiovascular risk is very high. Though this type of dietary intervention has been validated in Europe, it has not been well-studied in the United States, particularly in low-income, high-risk, minority populations. The lifestyle and weight loss interventions in our study led to improved reported overall diet quality, fat quality, fruit and vegetable consumption; and improved observed blood pressure and weight loss, though some subgroups of participants across diabetes status and race appeared to benefit more than others. The sustained weight loss among participants with diabetes at 24 months (3.67 kg) was the most noteworthy outcome. Participants with diabetes may have been more motivated to lose weight than those without diabetes.

The PREDIMED study documented efficacy of a similar dietary intervention however African Americans were not well represented in that study. PREDIMED study participants were 97% white. Because of the socioeconomic make-up of Lenoir County, residents have unique challenges compared to a largely European cohort. Despite these challenges, our tailored intervention led to improved cardiovascular intermediate outcomes such as reduced blood pressure, increased physical activity, improved diet quality, as well as weight loss.

Our intervention did not achieve the same degree of weight loss documented in the Diabetes Prevention Program (DPP) study,[18] which was over 5 kg at 24 months; however the study populations were very different. All participants in DPP were enrolled in an intensive weight loss intervention whereas fewer than half of participants in the HHLP lifestyle study opted to participate in the weight loss intervention. DPP also had more selective inclusion criteria and more exclusion criteria than HHLP. Furthermore, DPP enrolled participants without diabetes who had lower baseline weight; other studies have shown that individuals with higher BMI have more difficulty losing weight.[24,40,41] Incidentally, white participants with diabetes in the HHLP study still achieved similar weight loss (5.5 kg at 24 months) despite these differences. In fact, a meta-analysis of weight loss interventions among individuals with diabetes shows that the average weight loss using lifestyle interventions is much less than 3.7 kg at 24 months.[14] Unfortunately race data are not available as part of the meta-analysis however other studies have documented that whites tend to lose more weight on average than blacks with lifestyle interventions.[42]

Older participants and women are more likely to succeed with this type of counseling-based intervention format[43] and the study population is largely older women. Though we cannot account for all differences in baseline characteristics, a regression model adjusting for age, race, sex, education, and baseline weight did not show materially different outcomes compared to our unadjusted results.

The main limitation of the study is the lack of control group. Observed changes may be due to the intervention, by also may be due to secular trends. However, in the control groups of the DPP and Look AHEAD RCTs, weight loss at 2 years, on average, was less than one kilogram[15,18] suggesting that the weight loss is likely due to the intervention. In addition, from 2011 to 2014, there was no change in rates of overweight and obesity as assessed by the CDC's behavioral risk factor surveillance system.[44]   Another limitation is that lifestyle outcomes were self-reported and may have been exaggerated due to social desirability reporting bias.

Strengths of the study include its unselected sample with few exclusion criteria which enhances its generalizability. Furthermore, the fact that participants could choose their study arm allowed the study to mimic a real-world situation. The study enrolled over 300 participants with 74%

follow-up at 24 months, which is longer follow-up than most weight loss studies, with a substantial percentage of patients with diabetes. Physiologic outcomes were obtained using standardized objective measures. Finally, the weight loss observed in this study was more than most studies with 24 month follow-up.[14]

Conclusions

Although the majority of participants did not choose to participate in the weight loss intervention arm of the study, participants with diabetes across intervention arms achieved a sustained 3.67 kg weight loss at 24 months, as well as improved blood pressure, physical activity, diet quality, and a strong trend toward improvement in hemoglobin A1c. This study shows promise for a lifestyle intervention to improve cardiovascular risk, particularly among participants with diabetes, in a high-risk region of the United States. Therefore, further study is warranted with a randomized controlled trial to assess the benefits of this Mediterranean diet-based lifestyle intervention in high-risk populations.

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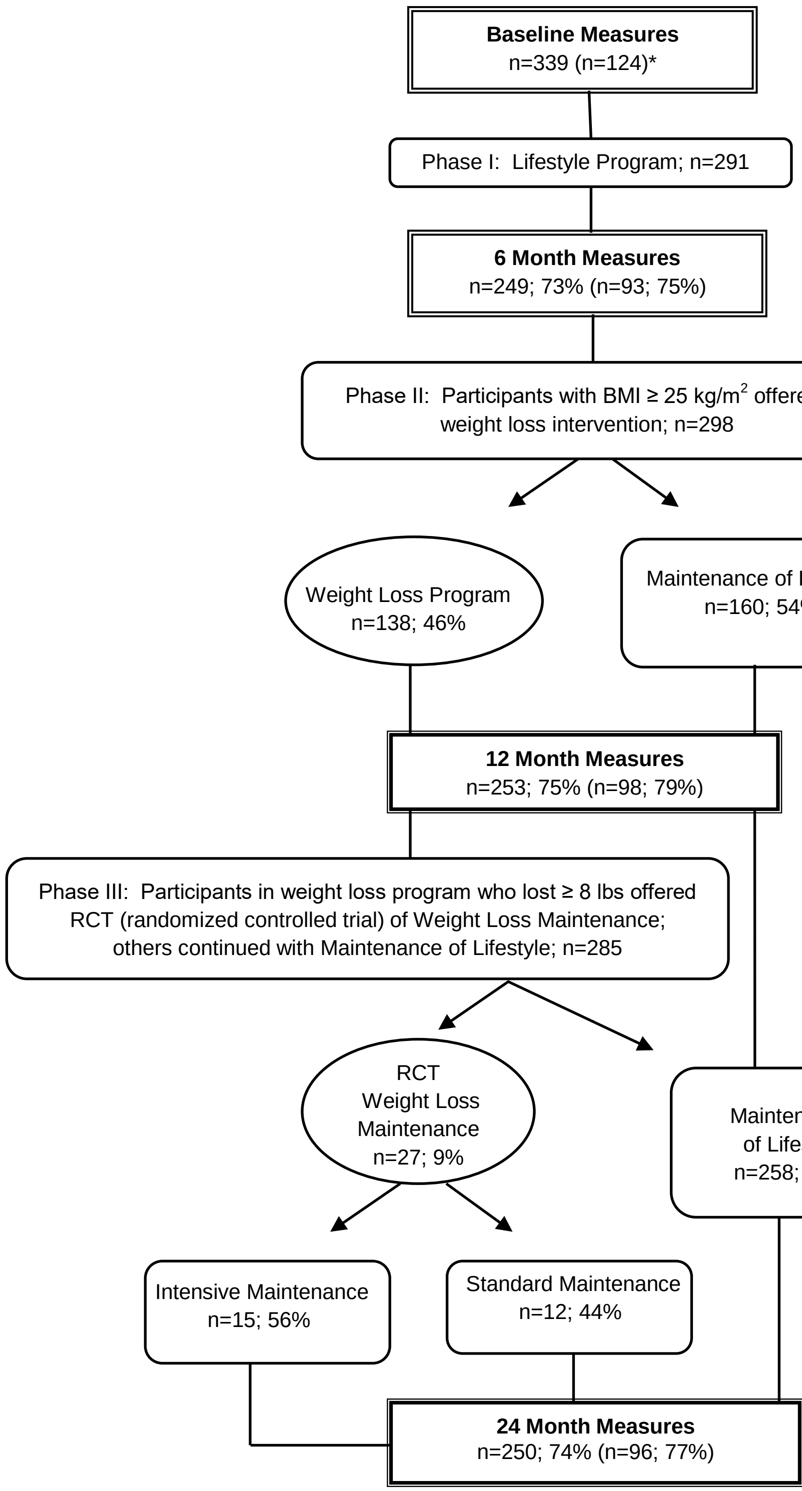

Fig. 1 Study overview

*Numbers in parentheses represent participants with diabetes and their respective follow-up rates at the end of each study phase.

Table 1. Baseline Characteristics: Overall, by Diabetes Status then by Race

	Overall	Diabetes			No Diabetes		
Characteristics		**All**	**Black**	**White**	**All**	**Black**	**White**
	n=339	n=124	n=89	n=34	n=215	n=130	n=83
Demographics							
Age, mean (SE)	56 (0.6)	59 (0.9)	59 (1.1)	61 (1.7)	54 (0.8)	51 (1.1)	57 (1.2)
Female	260 (77)	93 (75)	70 (79)	22 (65)	167 (78)	111 (85)	54 (65)
Race							
--Black	219 (65)	89 (72)			130 (60)		
--White	117 (35)	34 (27)			83 (39)		
Education, years							
-- ≤ 8 (middle school or less)	16 (5)	7 (6)	4 (5)	3 (9)	9 (4)	7 (5)	2 (2)
-- 9-11 (some high school)	45 (13)	25 (20)	22 (25)	2 (6)	20 (9)	13 (10)	7 (8)
-- 12 (high school graduate)	128 (38)	46 (37)	36 (40)	10 (29)	82 (38)	58 (45)	24 (29)
-- 13-15 (some college)	79 (23)	24 (19)	16 (18)	8 (24)	55 (26)	29 (22)	25 (30)
-- 16 (college graduate)	49 (14)	14 (11)	9 (10)	5 (15)	35 (16)	17 (13)	17 (21)
-- > 16 (graduate school)	22 (7)	8 (7)	2 (2)	6 (18)	14 (7)	6 (5)	8 (10)
Education: high school or less	189 (56)	78 (63)	62 (70)	15 (44)	111 (52)	78 (60)	33 (40)
Marital status							
-- Married or living with a partner	159 (47)	51 (41)	32 (36)	19 (56)	108 (50)	50 (39)	57 (69)
-- Other	180 (53)	73 (59)	57 (64)	15 (44)	107 (50)	80 (62)	26 (31)
Currently have health insurance	251 (74)	94 (76)	68 (76)	25 (74)	157 (73)	88 (68)	67 (81)
Current employment							
-- Working full-time	124 (37)	25 (20)	18 (20)	7 (21)	99 (46)	64 (49)	33 (40)
-- Working part-time	42 (12)	17 (14)	14 (16)	2 (6)	25 (12)	17 (13)	8 (10)
-- Do not work due to health reasons	69 (20)	38 (31)	26 (29)	12 (35)	31 (14)	17 (13)	14 (17)
-- Retired	53 (16)	26 (21)	18 (20)	8 (24)	27 (13)	8 (6)	19 (23)
-- Other	51 (15)	18 (15)	13 (15)	5 (15)	33 (15)	14 (19)	9 (11)
Annual household income							
-- < $10,000	62 (20)	31 (29)	24 (32)	6 (18)	31 (14)	26 (22)	5 (7)
-- $10,000 to < $20,000	64 (21)	28 (26)	23 (31)	5 (15)	36 (17)	22 (19)	14 (18)
-- $20,000 to < $40,000	84 (28)	29 (27)	20 (27)	9 (27)	55 (26)	40 (34)	14 (18)
-- $40,000 to < $60,000	33 (11)	9 (8)	3 (4)	6 (18)	24 (11)	12 (10)	12 (16)
-- $60,000 to < $80,000	27 (9)	9 (8)	4 (5)	5 (15)	18 (8)	9 (8)	9 (12)
-- ≥ $80,000	34 (11)	2 (2)	0 (0)	2 (6)	32 (15)	10 (8)	22 (29)
CVD and risk factors for CVD							
Known coronary heart disease	49 (14)	28 (23)	20 (23)	8 (24)	21 (10)	10 (8)	11 (13)
Known cardiovascular disease	62 (18)	33 (27)	23 (26)	10 (29)	29 (13)	14 (11)	15 (18)
Hypertension	291 (86)	121 (98)	88 (99)	32 (94)	170 (79)	107 (82)	63 (76)
Cholesterol							
-- High (≥240 mg/dL)	187 (56)	82 (67)	57 (65)	24 (71)	105 (49)	53 (42)	52 (63)
-- Borderline (200-239 mg/dL)	46 (14)	8 (7)	7 (8)	1 (3)	38 (18)	26 (21)	11 (13)
-- Desirable (<200 mg/dL)	102 (30)	33 (27)	24 (27)	9 (27)	69 (32)	48 (38)	20 (24)
Diabetes	124 (37)						
Current cigarette smoker	54 (16)	21 (17)	17 (19)	4 (12)	33 (15)	20 (15)	13 (16)
Packs of cigarettes smoked per day, mean (SE) for current smokers	0.7 (0.1)	0.6 (0.1)	0.6 (0.1)	0.8 (0.2)	0.7 (0.1)	0.6 (0.1)	0.9 (0.2)
Taking BP lowering medications	260 (77)	114 (92)	83 (93)	30 (88)	146 (68)	93 (72)	53 (64)

Lifestyle*							
DRA total score	27.8 (0.3)	28.5 (0.5)	28.3 (0.6)	28.9 (0.7)	27.4 (0.4)	27.2 (0.5)	27.7 (0.7)
Fat quality screener score	15.5 (0.2)	15.5 (0.2)	15.4 (0.3)	15.7 (0.3)	15.4 (0.2)	15.3 (0.2)	15.7 (0.4)
Fruit and vegetable servings per day	3.4 (0.1)	3.7 (0.2)	3.8 (0.2)	3.3 (0.3)	3.3 (0.1)	3.1 (0.2)	3.5 (0.2)
Walking time (min/wk)	91 (11.3)	67 (12.8)	68 (15.6)	54 (20.5)	105 (16.1)	122 (24.9)	80 (14.3)
Activity time (min/wk)	149 (14.0)	112 (18.1)	112 (20.5)	99 (36.0)	171 (19.3)	176 (27.1)	161 (26.3)
Physiologic*							
Weight, kg	98 (1.4)	103 (2.2)	103 (2.4)	104 (4.7)	95 (1.7)	99 (2.3)	90 (2.5)
BMI	36 (0.5)	38 (0.8)	38 (0.9)	38 (1.6)	35 (0.7)	37 (0.9)	32 (0.9)
Systolic blood pressure, mmHg	135 (1.2)	136 (2.0)	138 (2.4)	131 (3.6)	134 (1.5)	136 (2.1)	133 (2.2)
Diastolic blood pressure, mmHg	82 (0.7)	81 (1.1)	82 (1.4)	78 (1.9)	83 (0.8)	84 (1.1)	81 (1.2)
Hemoglobin A1c, %	6.6 (0.1)	7.9 (0.2)	8.0 (0.2)	7.6 (0.3)	5.8 (0.0)	5.8 (0.0)	5.7 (0.0)
Total cholesterol, mg/dL	193 (2.3)	188 (4.1)	188 (5.0)	187 (7.2)	196 (2.7)	193 (3.2)	200 (4.8)
HDL cholesterol, mg/dL	54 (0.8)	51 (1.4)	55 (1.6)	43 (2.1)	56 (1.0)	58 (1.3)	53 (1.6)

*mean (SE) recorded unless otherwise noted

Table 2. Change in Lifestyle Outcomes from Baseline to 6, 12, and 24 months

Outcome		Phase 1 Baseline to 6 months		Phase 2 Baseline to 12 months		Phase 3 Baseline to 24 months
	n	Mean, 95% CI	n	Mean, 95% CI	n	Mean, 95% CI
Dietary						
DRA total score	235	4.35 (3.68, 5.02)[a]	227	3.28 (2.54, 4.02)[a]	226	2.95 (2.28, 3.61)[a]
Diabetes (all)	86	4.19 (3.05, 5.33)[a]	86	3.04 (1.84, 4.24)[a]	84	2.03 (0.98, 3.09)[b]
--Black	60	4.41 (2.88, 5.94)[a]	63	3.80 (2.30, 5.31)[a]	62	2.46 (1.20, 3.72)[b]
--White	25	4.00 (2.63, 5.37)[a]	22	1.09 (-0.57, 2.75)	21	0.71 (-1.29, 2.72)
No diabetes (all)	149	4.43 (3.61, 5.26)[a]	141	3.42 (2.48, 4.37)[a]	142	3.49 (2.65, 4.32)[a]
--Black	95	4.72 (3.70, 5.74)[a]	93	4.14 (3.01, 5.26)[a]	96	3.34 (2.25, 4.42)[a]
--White	52	3.93 (2.47, 5.39)[a]	47	2.02 (0.31, 3.74)[d]	45	3.74 (2.48, 5.00)[a]
Fat quality screener score	229	1.39 (0.13, 1.75)[a]	225	0.97 (0.62, 1.32)[a]	224	0.66 (0.27, 1.05)[b]
Diabetes (all)	84	1.32 (0.67, 1.98)[a]	85	1.21 (0.64, 1.78)[a]	83	0.34 (-0.29, 0.96)
--Black	58	1.19 (0.36, 2.02)[c]	62	1.50 (0.77, 2.23)[a]	61	0.39 (-0.34, 1.12)
--White	25	1.56 (0.43, 2.69)[c]	22	0.41 (-0.34, 1.15)	21	0.14 (-1.19, 1.48)
No diabetes (all)	145	1.43 (1.00, 1.86)[a]	140	0.83 (0.39, 1.27)[b]	141	0.84 (0.35, 1.34)[b]
--Black	92	1.51 (0.98, 2.05)[a]	92	1.07 (0.55, 1.58)[a]	95	0.84 (0.28, 1.40)[c]
--White	51	1.24 (0.50, 1.97)[c]	47	0.40 (-0.43, 1.24)	45	0.87 (-0.14, 1.87)
Fruit and vegetable servings per day	249	0.29 (0.06, 0.51)[d]	253	0.54 (0.28, 0.80)[a]	250	0.38 (0.16, 0.61)[b]
Diabetes (all)	93	-0.06 (-0.50, 0.38)	98	0.18 (-0.30, 0.66)	96	0.05 (-0.35, 0.45)
--Black	67	-0.14 (-0.72, 0.45)	75	0.22 (-0.38, 0.83)	74	0.06 (-0.44, 0.55)
--White	25	0.13 (-0.38, 0.65)	22	-0.03 (-0.64, 0.57)	21	0.05 (-0.63, 0.73)
No diabetes (all)	156	0.49 (0.25, 0.74)[a]	155	0.76 (0.47, 1.05)[a]	154	0.59 (0.33, 0.86)[a]
--Black	101	0.51 (0.21, 0.82)[c]	103	0.76 (0.38, 1.14)[a]	103	0.56 (0.21, 0.90)[c]
--White	53	0.45 (0.02, 0.88)[d]	51	0.76 (0.33, 1.20)[b]	50	0.64 (0.23, 1.06)[c]
Summary score for drinks, desserts, snacks	236	1.10 (0.85, 1.34)[a]	229	1.34 (1.07, 1.61)[a]	228	1.08 (0.82, 1.33)[a]
Diabetes (all)	87	1.06 (0.71, 1.40)[a]	87	1.18 (0.79, 1.58)[a]	85	0.92 (0.53, 1.31)[a]
--Black	61	1.11 (0.67, 1.56)[a]	64	1.25 (0.77, 1.73)[a]	63	1.14 (0.71, 1.57)[a]
--White	25	1.00 (0.48, 1.52)[b]	22	1.05 (0.31, 1.78)[c]	21	0.14 (-0.68, 0.97)
No diabetes (all)	149	1.12 (0.79, 1.46)[a]	142	1.43 (1.07, 1.79)[a]	143	1.17 (0.83, 1.51)[a]
--Black	95	1.33 (0.89, 1.76)[a]	93	1.66 (1.18, 2.14)[a]	96	1.32 (0.88, 1.76)[a]
--White	52	0.71 (0.20, 1.22)[c]	48	0.92 (0.43, 1.41)[b]	46	0.78 (0.31, 1.26)[c]

Physical Activity						
Walking time, min/wk	249	64.17 (19.23, 109.12)[c]	253	70.75 (28.36, 113.15)[c]	250	21.76 (-12.72, 56.23)
Diabetes (all)	93	100.69 (16.90, 184.47)[d]	98	126.00 (57.57, 194.43)[b]	96	61.90 (10.71, 113.08)[d]
--Black	67	119.31 (17.52, 221.11)[d]	75	135.77 (51.72, 219.83)[c]	74	74.91 (12.52, 137.29)[d]
--White	25	70.80 (-81.24, 222.84)	22	116.59 (14.15, 219.04)[d]	21	38.05 (-36.18, 112.27)
No diabetes (all)	156	42.40 (-8.78, 93.59)	155	35.82 (-17.44, 89.08)	154	-3.27 (-48.79, 42.26)
--Black	101	28.81 (-44.88, 102.50)	103	18.70 (-53.49, 90.88)	103	-17.26 (-81.99, 47.47)
--White	53	63.11 (7.89, 118.33)[d]	51	67.57 (-3.24, 138.38)	50	21.90 (-21.87, 65.67)
Activity time, min/wk	249	96.76 (35.65, 157.87)[c]	253	83.03 (30.21, 135.85)[c]	250	48.09 (-7.12, 103.29)
Diabetes (all)	93	120.25 (19.24, 221.26)[d]	98	108.51 (28.95, 188.07)[c]	96	61.67 (-8.09, 131.42)
--Black	67	135.72 (16.81, 254.62)[d]	75	127.32 (32.04, 222.60)[c]	74	88.80 (2.76, 174.83)[d]
--White	25	105.60 (-94.27, 305.47)	22	74.32 (-63.00, 211.64)	21	-4.81 (-90.53, 80.91)
No diabetes (all)	156	82.76 (6.10, 159.41)[d]	155	66.92 (-2.97, 136.81)	154	39.62 (-38.70, 117.95)
--Black	101	85.89 (-17.24, 189.03)	103	36.97 (-41.94, 115.88)	103	28.27 (-75.52, 132.06)
--White	53	79.34 (-32.89, 191.57)	51	125.18 (-15.11, 265.46)	50	57.80 (-55.44, 171.04)

[a] $p \leq 0.0001$
[b] $p \leq 0.001$
[c] $p < 0.01$
[d] $p < 0.05$

Table 3. Change in Physiologic Outcomes from Baseline to 6, 12, and 24 months

		Phase 1		Phase 2		Phase 3
		Baseline to 6 months		Baseline to 12 months		Baseline to 24 months
Outcome	n	Mean, 95% CI	n	Mean, 95% CI	n	Mean, 95% CI
Systolic BP, mmHg	249	-6.39 (-8.69, -4.09)[a]	251	-6.15 (-8.99, -3.31)[a]	250	-7.25 (-9.93, -4.57)[a]
Diabetes (all)	93	-7.14 (-11.28, -2.99)[b]	97	-5.75 (-10.93, -0.57)[d]	96	-7.44 (-11.92, -2.97)[c]
--Black	67	-8.58 (-13.93, -3.22)[c]	74	-6.39 (-12.69, -0.08)[d]	74	-9.29 (-14.57, -4.02)[b]
--White	25	-3.83 (-9.63, 1.98)	22	-4.11 (-13.19, 4.96)	21	-0.39 (-8.73, 7.95)
No diabetes (all)	156	-5.94 (-8.65, -3.24)[a]	154	-6.40 (-9.68, -3.11)[b]	154	-7.13 (-10.47, -3.79)[a]
--Black	101	-5.56 (-8.91, -2.21)[c]	102	-7.34 (-11.58, -3.10)[b]	103	-7.85 (-12.22, -3.49)[b]
--White	53	-6.45 (-11.26, -1.65)[c]	51	-4.31 (-9.46, 0.84)	50	-5.60 (-10.66, -0.54)[d]
Diastolic BP, mmHg	249	-3.73 (-4.93, -2.53)[a]	251	-4.98 (-6.38, -3.57)[a]	250	-6.72 (-8.29, -5.15)[a]
Diabetes (all)	93	-4.36 (-6.40, -2.32)[a]	97	-5.61 (-8.19, -3.02)[a]	96	-7.18 (-10.10, -4.26)[a]
--Black	67	-4.63 (-7.17, -2.10)[b]	74	-5.77 (-8.81, -2.72)[b]	74	-8.18 (-11.70, -4.66)[a]
--White	25	-4.12 (-7.57, -0.67)[d]	22	-4.72 (-10.00, 0.56)	21	-3.33 (-8.30, 1.65)
No diabetes (all)	156	-3.35 (-4.82, -1.89)[a]	154	-4.58 (-6.19, -2.98)[a]	154	-6.44 (-8.21, -4.66)[a]
--Black	101	-2.82 (-4.76, -0.87)[c]	102	-4.81 (-6.95, -2.68)[a]	103	-6.47 (-8.91, -4.03)[a]
--White	53	-4.29 (-6.51, -2.07)[b]	51	-3.92 (-6.22, -1.63)[b]	50	-6.33 (-8.53, -4.14)[a]
Weight, kg	248	-0.71 (-1.17, -0.26)[c]	250	-1.72 (-2.47, -0.96)[a]	247	-1.63 (-2.51, -0.75)[b]
Diabetes (all)	92	-1.24 (-2.10, -0.38)[c]	96	-1.53 (-2.89, -0.17)[d]	93	-3.67 (-5.19, -2.14)[a]
--Black	66	-1.13 (-1.96, -0.29)[c]	73	-1.03 (-2.45, 0.39)	71	-3.07 (-4.61, -1.52)[b]
--White	25	-1.64 (-3.95, 0.67)	22	-3.26 (-6.90, 0.38)	21	-5.53 (-9.85, -1.21)[d]
No diabetes (all)	156	-0.40 (-0.91, 0.11)	154	-1.83 (-2.71, -0.95)[a]	154	-0.40 (-1.42, 0.62)
--Black	101	-0.67 (-1.37, 0.04)	102	-2.23 (-3.37, -1.08)[b]	103	-0.94 (-2.24, 0.35)
--White	53	0.17 (-0.48, 0.81)	51	-0.96 (-2.29, 0.37)	50	0.86 (-0.76, 2.48)
≥5% weight loss, %	248	9.27 (5.64, 12.91)	250	23.20 (17.93, 28.47)	247	23.08 (17.79, 28.37)
Diabetes (all)	92	10.87 (4.47, 17.27)	96	20.83 (12.65, 29.01)	93	34.41 (24.69, 44.13)
--Black	66	12.12 (4.10, 20.15)	73	19.18 (9.98, 28.38)	71	32.39 (21.30, 43.49)
--White	25	8.00 (0.00, 18.84)	22	27.27 (8.32, 46.23)	21	38.10 (16.93, 59.26)
No diabetes (all)	156	8.33 (3.97, 12.70)	154	24.68 (17.82, 31.53)	154	16.23 (10.37, 22.10)
--Black	101	11.88 (5.50, 18.26)	102	26.47 (17.81, 35.13)	103	18.45 (10.87, 26.02)
--White	53	1.89 (0.00, 5.59)	51	19.61 (8.59, 30.63)	50	10.00 (1.59, 18.41)
HgA1c, %	217	0.01 (-0.09, 0.12)	220	-0.07 (-0.20, 0.06)		
Diabetes (all)	80	-0.11 (-0.38, 0.17)	84	-0.30 (-0.63, 0.02)		
--Black	60	-0.10 (-0.45, 0.25)	66	-0.33 (-0.72, 0.06)		
--White	19	-0.20 (-0.60, 0.20)	17	-0.28 (-0.85, 0.28)		
No diabetes (all)	137	0.08 (0.04, 0.11)[a]	136	0.07 (0.01, 0.13)[d]		
--Black	87	0.10 (0.05, 0.14)[a]	88	0.08 (0.01, 0.16)[d]		
--White	48	0.05 (0.00, 0.10)	47	0.05 (-0.03, 0.13)		

[a] $p \leq 0.0001$
[b] $p \leq 0.001$
[c] $p < 0.01$
[d] $p < 0.05$

Literature Review: Does a Mediterranean Diet Reduce Cardiovascular Disease?

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in the United States[1] and worldwide,[2] and is therefore a major public health concern. Although there are numerous factors that contribute to the incidence of CVD, diet has been long recognized as a modifiable risk factor. From a public health perspective, prevention of CVD is the ideal approach to reduce deaths and nonfatal events such as myocardial infarctions (MI) and cerebrovascular accidents (CVA), or strokes. Prevention is also crucial to curbing the unsustainable associated health care costs for interventions including hospitalizations, procedures, medications, and long-term care for debility after non-fatal CVD events.

CVD is particularly prevalent in the Southeastern United States,[3] much of which is aptly named the "stroke belt." Overall diet quality is poor in the stroke belt;[4,5] access to healthy foods is a real problem in rural communities; and residents are more likely to be of low socioeconomic status, obese, sedentary, and African American. All of these are risk factors for CVD. Diet quality is a modifiable risk factor that contributes to obesity and diabetes which are stronger risk factors for CVD. Prior studies have shown that lifestyle interventions can be effective in achieving weight loss and improving intermediate outcomes but few have demonstrated a reduction in cardiovascular events.[6,7]

Historically, dietary recommendations including those from national organizations such as the American Heart Association have focused on reducing fat, particularly saturated fat, from the diet.[8] However, randomized controlled trials studying the effects of a low-fat diet on cardiovascular health have failed to show reduced CVD events.[6,7,9] In fact, there is concern that promoting a low-fat diet may contribute to increased consumption of carbohydrates that may ultimately worsen rates of obesity and diabetes, and may increase the risk of CVD.[10]

Some studies have promoted a Mediterranean diet. Mediterranean diets have common features – an emphasis on vegetables, fruits, beans, nuts, seeds, breads, unrefined grains, and olive oil; inclusion of fish and wine; and minimal intake of meats and full-fat dairy products.[11] The olive oil, nuts, and fatty fish would not be recommended as part of a strictly low-fat dietary pattern. Despite this, studies evaluating a Mediterranean-based diet seem to be the most promising in terms of reducing CVD,[12] hence the question, "Does a Mediterranean diet reduce cardiovascular disease?"

Methods

Search Strategy

An electronic search of PubMed and Google Scholar were used to identify relevant studies. PubMed was searched using the MeSH terms "Mediterranean diet" and "cardiovascular diseases." The search was supplemented by reviewing references from identified articles and reviews.

Article Selection

Selected articles were limited to those published in English, involving human subjects, and with full text availability. The search was also narrowed to include only clinical studies or trials (including randomized controlled trials and comparative studies). Titles and abstracts were reviewed to confirm relevance to the question. Specifically, studies needed to use a traditional Mediterranean diet and evaluate CVD outcomes (including cardiovascular death, MI, or CVA). Studies that assessed intermediate outcomes only (e.g. laboratory markers, blood pressure, lipid profiles, etc) were excluded. Studies that used a modified Mediterranean diet were excluded. Titles that were clearly not relevant were excluded (e.g. looking at cancer outcomes in pts with high cardiovascular risk instead of cardiovascular outcomes). If the relevance was unclear, abstracts were reviewed more thoroughly. To narrow the search further, only articles that were published after 2006 underwent full text review for this limited literature review. Articles that included a traditional Mediterranean diet and identified at least one cardiovascular outcome (including cardiac mortality, MI, CVA, congestive heart failure (CHF)) published after 2006 underwent full text review. If multiple studies were published by the same author group using the same data set from the same study or trial, only the main cardiovascular results paper was used instead of looking at smaller articles with more segmented samples and outcomes.

Data Abstraction and Evaluation

Articles were read for analytical consideration of the quality of findings, including strengths and limitations by a single author (GGRE) to assess internal and external validity. Considerations included study design (e.g. randomized controlled trials were considered more favorable than observational studies), confounders, bias, effect magnitude and precision, as well as clarity about the definition of a "traditional Mediterranean diet." The traditional Mediterranean diet consists of high intake of olive oil, vegetables, fruit, nuts, and whole-grain cereals; moderate intake of fish, poultry, and low-fat dairy; and low intake of red meat, processed meats, and sweets. Wine is consumed in moderation with meals.

Results

The search strategy yielded 749 results using both "Mediterranean diet" and "cardiovascular diseases." The results were filtered for language, human subjects, full text availability, and clinical studies or trials yielding 198 articles. Title review for relevance narrowed the search to 24 articles and abstract review narrowed it further to 9 articles. Only 5 of those were published after 2006 and therefore underwent full text review. These five articles were deemed to have acceptable study design and unique data. The process by which the literature search was performed is summarized in Figure 1.

Of the five articles chosen for review, two were randomized controlled trials (RCT) that compared a Mediterranean diet to a low-fat diet.[13,14] The PREDIMED trial was a very well-designed large RCT.[13] The other RCT also included a no dietary intervention control group however that comparison used an embedded case-control format.[14] One other article was also a case-control study.[15] The final two studies were retrospective analyses of large cohort studies: the Nurses' Health Study[16] and the Seguimiento Universidad de Navarra (SUN) project.[17] Overall quality of the studies was fair due to mostly retrospective study designs, measurement bias, and poor external validity. Many of the studies did have large sample sizes. There were well-defined outcomes and the direction of the findings was consistent across studies with similar magnitude though specific outcomes measures were different across studies. Authorship, publication information, study design, population, methods, and results are outlined in Table 1.

Analysis

The first article by Estruch et al.[13] was a randomized controlled trial, PREDIMED, with over 7,000 study participants that compared a Mediterranean diet supplemented with either 4 tablespoons of extra virgin olive oil per day or 30 grams of nuts per day to a control lower-fat diet to see if the intervention diets improved cardiovascular outcomes compared to the control diet with a composite endpoint of MI, CVA, and cardiovascular mortality. As a randomized controlled trial, it has a much stronger study design than any of the other articles and still has a large, respectable sample size. It is different from some of the other studies in that it does not have a “no intervention” or no recommendation dietary control group. All study participants were recommended to adhere to some dietary pattern. This study was also notable for the magnitude of the effect. In fact, the study was stopped early because of the magnitude of the findings.

PREDIMED enrolled participants who were deemed to be at high CVD risk by the presence of either diabetes or at least three other cardiovascular risk factors (including smoking, hypertension, elevated LDL levels, low HDL levels, overweight or obesity, and a family history of premature coronary heart disease). Participants were older on average than the other studies with an age range of 55-70. It was also a primary prevention study so participants did not have CVD at baseline (which differs from the other RCT).

The study found that intervention arms had a 30% reduced risk of CVD compared to controls. These findings went against a lot of popular beliefs that a “healthy” diet should be low-fat. In fact, the Mediterranean dietary intervention used in this study was calorie unrestricted and actually encouraged the use of high-fat supplemental extra virgin olive oil (EVOO) and nuts in the two intervention arms, respectively. Yet, even with these higher fat intervention diets, the magnitude of the findings was significant. Other strengths are that the RCT study design suggests a causal role for a Mediterranean diet in cardiovascular disease prevention and eliminates confounding.

A limitation of the study is that the findings may not be generalizable to individuals who do not have a high baseline cardiovascular risk profile, although the diet may reduce CVD risk across different baseline risks. Also, the study demonstrated efficacy of both intervention arms with supplemental EVOO and nuts; however, it's unclear how effective the diet is in a real-world situation where individuals are not given free EVOO and nuts to consume. Observed rates of cardiovascular events were lower than expected so the study was not powered to assess the individual components of the primary composite outcome. Finally, because the study was performed in Spain where many may eat a Mediterranean diet at baseline, the between-group differences were modest aside from the supplemental EVOO and nuts which suggests that those may be responsible for the observed benefits rather than providing evidence that the Mediterranean diet as a whole was responsible for the observed outcomes.

The second article by Kastorini et al.[15] was a multi-center case-control study that enrolled 250 participants each with first acute coronary syndrome or ischemic stroke with 500 age- and sex-matched controls. Their study looked at the association between adherence to a Mediterranean diet and incidence of a first coronary event or ischemic stroke. Although all of the studies included in this review included strokes in their measured outcomes, this study was notable for focusing on the association between adherence to a Mediterranean diet and stroke specifically; therefore, odds ratios were calculated separately for stroke incidence.

It was a multi-center study that enrolled consecutive individuals with first time MI or ischemic stroke without suspicion of previous CVD and 1:1 matched controls. They had relatively few exclusion criteria which were comorbid chronic neoplasm, chronic inflammatory disease, and recent dietary changes. ACS cases were younger and more likely to be male than CVA cases. Controls had higher baseline MedDietScores, were more physically active, and less likely to smoke. They also had lower prevalence of diabetes, hypertension, and family history of CVD. After controlling for potential confounders, the study authors found a 0.91 and 0.88 odds of developing ACS and ischemic CVA, respectively, for each 1-unit increase in MedDietScore (out of 55) which assesses adherence to a Mediterranean diet.

Limitations of this study include its retrospective design and inability to control for all potential confounders. Dietary reporting is subject to recall bias. Additionally, the diet log was recorded during the first 3 days of hospitalization which may not represent a typical diet for those participants. Furthermore, people with disease will tend to over-report unhealthy dietary habits. The study is subject to survivor bias. Finally, bias may have been introduced for stroke patients who could not communicate well and required a surrogate to answer study questions for them.

The third article by Martinez-Gonzalez et al.[17] was a cohort study that used data from the Seguimiento Universidad de Navarra (SUN) project with over 13,000 participants to evaluate the association between Mediterranean diet adherence and incident cardiovascular disease (including cardiovascular death, acute coronary syndrome (ACS), revascularization procedures, and fatal or non-fatal CVA). Notable considerations about this study were that the study population was much younger than other studies because it was drawn from a cohort of university graduates; therefore despite the large cohort size, there were relatively few incident cases.

Mean age of study participants was 38. Participants with baseline prevalent CVD were excluded. Median follow-up was 4.9 years and there were 100 cases of incident CVD. Higher adherence scores were associated with increased physical activity profiles but also with risk factors for CVD: being an ex-smoker or having diabetes, hypertension, dyslipidemia, or a family history of coronary disease at baseline. Multiple multi-variable-adjusted models all showed an inverse association between Mediterranean diet adherence and incident CVD. A 2-point increment in Mediterranean diet score (out of 9) was associated with a 20% reduction in risk of CVD and 26% reduction in incidence of coronary heart disease.

Limitations include the small number of incident events. It's also unclear how participants all being university graduates would affect its generalizability. This study was inconsistent with some of the other literature in several ways. They found cereal associated with increased CVD risk however their diet score does not differentiate between whole grain and refined cereals. Additionally, their principal component analysis yielded two vectors, one of which they called the "post hoc Mediterranean pattern" as it correlated with the consumption of vegetables, fruits, fish, poultry, low-fat dairy, whole grains, nuts, olive oil, and legumes; interestingly, this dietary pattern has a non-significant positive association with CVD.

The fourth article by Fung et al.[16] was also a cohort study. This study used data from Nurses' Health Study with almost 75,000 women that evaluated the association between a Mediterranean diet adherence score and incident coronary heart disease and stroke. This study was notable for the fact that they were able to assess dietary adherence at multiple time points over a 6-year period which may make it more reliable. They were also able to follow participants over a much longer period of time (up to 20 years) and they had high follow-up rates despite the long duration of the study.

Participants in the Nurses' Health Study were women age 30 to 55 years at the time of enrollment in the United States. During up to 20 years of follow-up, they ascertained 2391 cases of coronary heart disease (CHD) and 1763 cases of stroke. At baseline, women with higher Mediterranean diet adherence scores (aMed score) exercised more and were less likely to be smokers; they consumed more calories and fiber but less saturated fat. After adjusting for potential confounders, they found that women in the top quintile of aMed score had a relative risk (RR) of 0.71 compared to those in the bottom quintile. A similar inverse association was observed for strokes with RR 0.87 for top quintile compared to bottom quintile. Associations were stronger for fatal events.

Limitations include residual confounding as it is an observational study and lack of generalizability to men since the study only enrolled women. High follow-up rates reduced the probability of selection bias; repeated dietary assessments over time reduce the risk of measurement bias.

The fifth article by Tuttle et al.[14] was a combination randomized controlled trial and case-control study. The RCT compared a Mediterranean diet to a low-fat diet in 101 participants and the controls in the case-control had no dietary intervention or recommendation. This study assessed the efficacy of a Mediterranean diet versus a low-fat diet in secondary prevention of cardiovascular disease (including ACS, CVA, hospitalization for heart failure, cardiac death, and all-cause mortality). This study is notable because it assessed secondary prevention of CVD whereas the other studies in this literature review looked at primary prevention. It is also notable because it tests a clinically-relevant comparison of whether Mediterranean or low-fat diet leads to better cardiovascular outcomes after MI in a prospective, randomized trial.

Participants in this study all had a first MI as part of the inclusion criteria and were mostly middle-aged white men. The study found no significant difference between the Mediterranean diet and a low-fat diet in secondary prevention of CVD however it demonstrated that both a Mediterranean diet and low-fat diet had reduced incidence of CVD compared to “usual care” or no dietary intervention with an adjusted OR of 0.28.

A major limitation is the broad and non-specific composite primary outcome including all-cause mortality and heart failure. In fact, the only 2 outcomes that were statistically significant individually were unstable angina and all-cause mortality (which may not have been related to CVD at all). Other limitations include the small sample sizes and small number of CVD events (only 8 events in each RCT group). This study may not be generalizable to populations without pre-existing CVD; individuals with pre-existing CVD may be more motivated to follow a dietary intervention and therefore the outcomes may be exaggerated. There is significant selection bias as the true controls (that led to the only significant findings) were case-controls instead of a third arm in the RCT. The study was designed that way because referring physicians had indicated that they would not refer their patients to the study if there was a risk of being assigned to a non-intervention arm after an MI. They felt it would be unethical as prior studies had shown benefit to dietary modification after MI.

Discussion

Overall strength of the evidence for a Mediterranean diet reducing the risk of cardiovascular disease is fairly good. The studies included in this literature review each have limitations but the direction of the findings is consistent across all of the studies, suggesting that a Mediterranean diet does in fact reduce the risk of cardiovascular disease. Study samples are heterogeneous (some younger; some older; some only have women; most with no prior CVD and a range of CVD risk factors; one where all participants had prior CVD) in addition to sampling from populations in different regions of the world. Two of the five studies were very good quality studies. Some had inherent problems with the study designs. Only one study was a large, multi-center randomized controlled trial with minimal selection and measurement bias however even that study (PREDIMED) was unable to confidently attribute the positive outcomes to the Mediterranean diet as a whole; rather they suggested the reduction in CVD may be attributable to the supplemental EVOO and nuts.[13] That being said, the traditional Mediterranean diet has been consistently associated with reduced CVD and mortality, across studies, including those performed before 2006, not included in this literature review. The findings in the included articles in this review are consistent with the literature prior to 2006.[18,19] One inherent challenge with any study or trial looking at a Mediterranean diet, or any diet for that matter, is measurement bias from either recall bias or social desirability reporting bias. Dietary surveys and even food diaries have not been shown to be fully accurate or representative of an individual's overall diet quality;[20] however, valid, reliable, accurate, and affordable alternatives are lacking to provide a perfect representation of true diet. There are some biomarkers that can give a more objective indication of dietary adherence and quality however levels can change over time and the tests can be expensive.

Slight discrepancies in adherence measurement tools and study designs make it still unclear which aspects of the Mediterranean diet or which combinations of the many dietary components of the Mediterranean diet are most beneficial in reducing CVD. The magnitude of the protective effect of a Mediterranean diet in the United States is still yet to be determined with a large, multi-center, randomized controlled trial.

One interesting finding across several of the studies was that the inverse association between a Mediterranean diet and mortality (both disease-specific and overall) tended to be stronger than the inverse association between the Mediterranean diet and the disease itself. This suggests that the diet may mediate cardiovascular disease through a mechanism that is common to other diseases as well that can also result in death. For example, some studies have shown that a Mediterranean diet can reduce inflammatory markers that may play a role in multiple disease processes.

A causal protective relationship was suggested by the PREDIMED randomized controlled trial.[13] To determine the absolute effect a Mediterranean diet has on preventing CVD in the United States, future studies should have a randomized controlled trial study design. Future studies could be modeled after PREDIMED but with a no intervention control arm and a more “pure” intervention arm with no supplemental oils or nuts, to make the study more externally valid. Basing the large RCT in the United States would show benefits relative to a standard U.S. diet (whereas the baseline diet for the intervention and control groups were too similar in PREDIMED which was based in a Mediterranean region).

Conclusion

When taken together, the data from these studies strongly suggest that a Mediterranean diet does reduce the risk of CVD.

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Figure 1. Study selection flow diagram

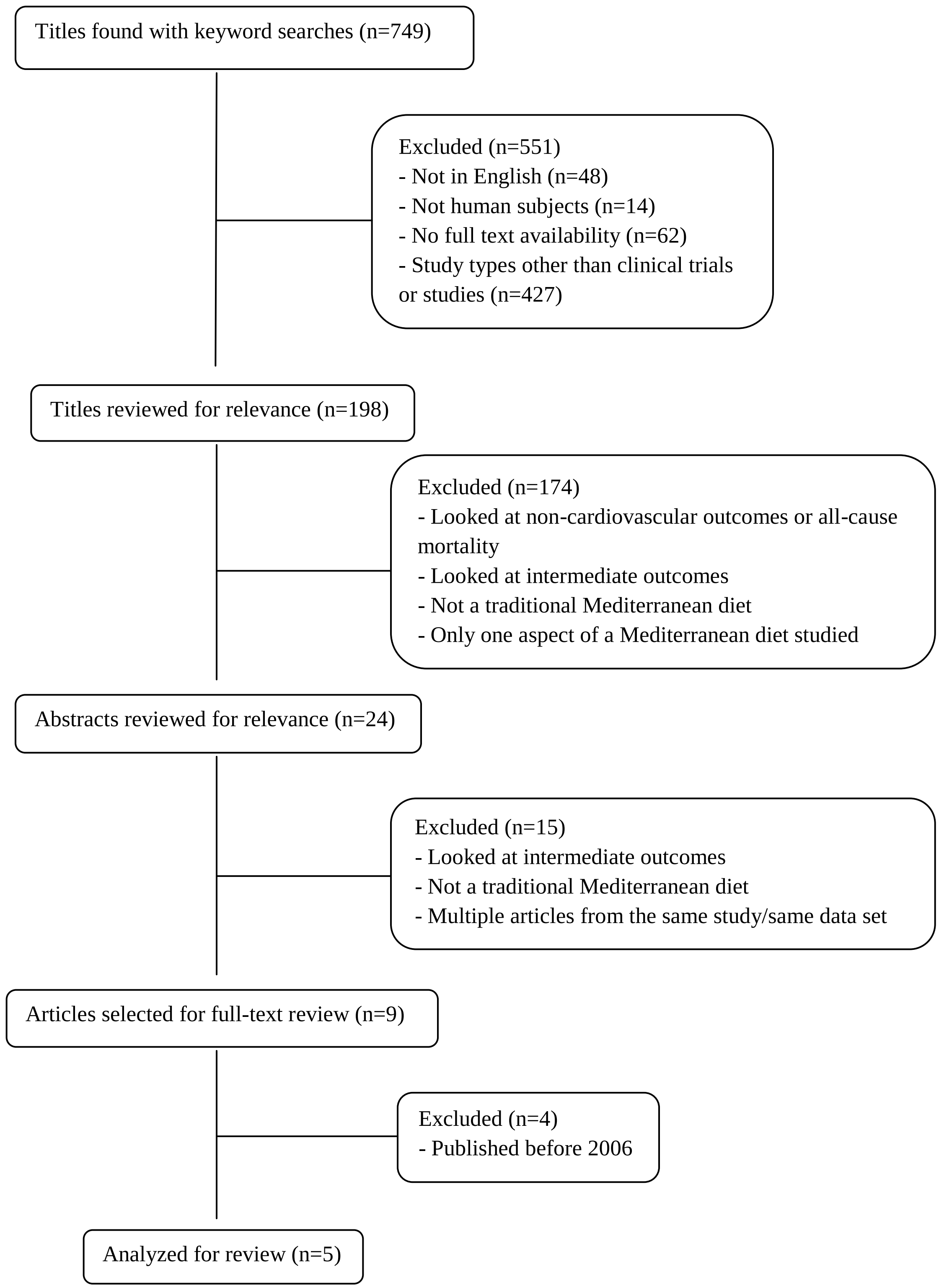

Table 1. Study profiles

Study citation	Design	Population	Methods	Outcome measure	Results	Quality rating
Estruch R, Ros E, Salas-Salvado J, et al. NEJM 2013[13]	Multi-center randomized controlled trial	7,447 participants in Spain ages 55-70 with no CVD at enrollment but high-risk: either +DM or 3+ other CVD risk factors	Randomly assigned to 1 of 3 diets: Med diet + EVOO, Med diet + mixed nuts, or low-fat control diet; also received dietary education	Composite: MI, CVA, and death (from cardiovascular causes)	HR 0.70 for Med diet + EVOO and HR 0.72 for Med diet + mixed nuts (compared to controls)	Excellent
Kastorini C-M, Milionis HJ, Ioannidi A, et al. American Heart Journal 2011[15]	Multi-center case-control study	1,000 participants in Greece: 250 with first ACS, 250 with first ischemic CVA (without suspicion of previous CVD) and 500 age- and sex-matched controls	Assessed adherence to a Med diet using validated MedDietScore from dietary recall and 3-day food record	First ACS or first ischemic CVA	OR 0.91 for ACS and OR 0.88 for each 1-unit increase in the MedDietScore (out of 55)	Fair
Martinez-Gonzalez MA, Garcia-Lopez M, Bes-Rastrollo M, et al. Nutrition, Metabolism, & Cardiovascular Diseases 2011[17]	Cohort study	13,609 university graduates in Spain (part of the SUN project) initially free of CVD (average age 38)	Used a food-frequency questionnaire to assess baseline diet then appraised adherence to Med diet using a 9-point score	Combined: incident cardiovascular death, ACS, revascularization procedures, fatal CVA, or non-fatal CVA	HR 0.41 for Med Diet adherence score > 6 (compared to < 3); adjusted HR 0.80 for each 2-unit increase in adherence score (out of 9)	Fair
Fung TT, Rexrode KM, Mantzoros CS, et al. Circulation 2009[16]	Cohort study	74,886 women age 38-63 in the Nurses' Health Study with no history of CVD or DM	Computed an Alternate Mediterranean Diet Score from self-reported dietary data through food frequency questionnaires administered 6 times over 20 years	Incident cases of CHD (nonfatal MI or fatal CHD) and CVA	2391 incident CHD, 1763 incident CVA, 1077 CVD deaths → RR 0.71 for CHD, RR 0.87 for CVA, RR 0.61 for CVD mortality (comparing top Med Diet score quintile to bottom quintile)	Very good
Tuttle KR, Shuler LA, Packard DP, et al. American Journal of Cardiology 2008[14]	Randomized controlled trial comparing Med diet to low-fat diet + case-control analysis to compare to no dietary intervention (usual care)	101 first MI survivors participated in RCT; controls in case-control analysis were matched for age, gender, MI type/treatment, diabetes status, and hypertension status	Randomized to low-fat or Mediterranean-style diet; also received individual dietary counseling	Composite: all-cause deaths, cardiac deaths, MI, hospital admission for heart failure, unstable angina, or CVA	No difference between Med diet and low-fat diet but both were better than usual care (adjusted OR 0.28)	Fair